



FDA Regulation of In Vitro Diagnostic Tests

**FDA Public Meeting on Oversight of
Laboratory Developed Tests**

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Agenda

- General introduction to FDA and IVD regulation
- How does FDA regulate IVDs?
 - Device Classification
 - Premarket Review
 - Postmarket Requirements
- Information and Resources

Legal Basis of Regulation

- Authority to regulate medical devices
 - Public Health Services Act
 - Federal Food Drug and Cosmetic Act (FFDCA) of 1938
 - Medical Device Amendments 1976
- Other legislation
 - FDA Modernization acts of 1997, 2002 and 2007

FDA Regulation of Medical Devices

- 1976 Device Amendments modified the Act to provide for the regulation of Medical Devices
 - Medical Devices: “an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent or similar related article. . . intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals” (FFDCA 201(h))

Definition of IVDs

- IVDs are a subset of medical devices which are “**reagents, instruments, and systems** intended for use in the **diagnosis of disease or other conditions**, including a determination of the state of health, in order to cure, **mitigate, treat, or prevent disease or its sequelae**” (21 CFR 809.3)

Risk-Based Classification of IVDs: Intended Use

- The classification of an IVD is risk-based, and determined based upon the intended use of the device
- Intended Use:
 - General description of the disease or condition that the device will diagnose, treat, prevent cure or mitigate
 - Defines the patient population
 - Defines specific type of specimen
- A single IVD can have multiple intended uses

Intended Use Statement (2)

- Example: Pregnancy Test

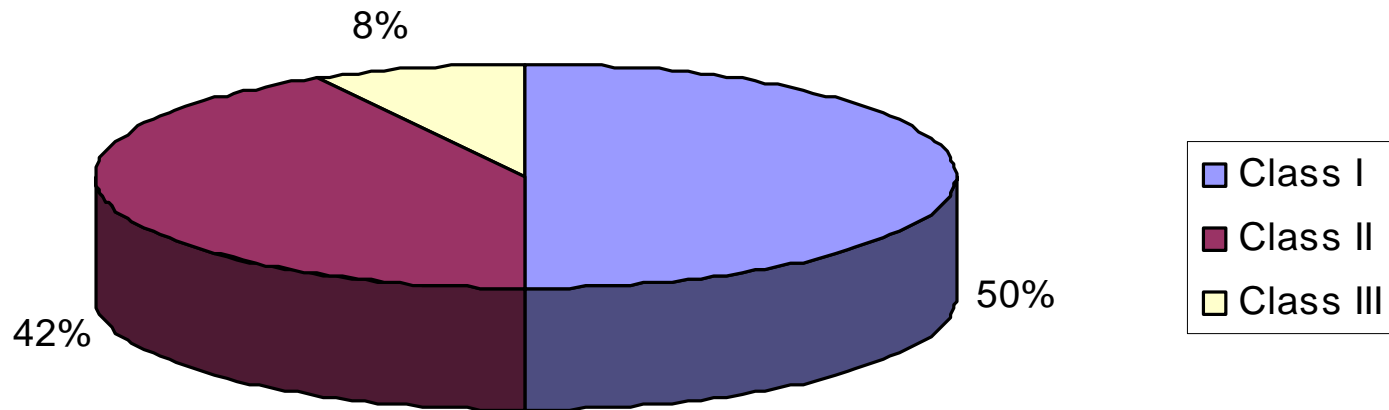
“The X urine test is an immunoassay designed for the qualitative determination of human chorionic gonadotropin (hCG) in urine for the early detection of pregnancy. It is intended for professional use.”

Risk-Based Classification of IVDs

- The risk of an IVD is based on the consequences of a false result
- 3 Classification levels
 - Class I: common, low risk devices
 - Class II: more complex, moderate risk
 - Class III: most complex, high risk and novel intended uses

IVDs: Classification Breakdown

Percentage of IVD Devices by Product Class



Class I IVDs

- Represent common, low-risk devices
- Examples:
 - lactic acid
 - erythrocyte sedimentation rate test
 - differential culture media
- Most exempt from premarket submission
- General Controls are required

General Controls

- Applicable to medical devices, regardless of class
- Registration and listing
 - Manufacturers must register their manufacturing facilities, and list the devices they manufacture
- Good Manufacturing Practices (GMP)
 - Devices must be manufactured in a controlled manner as per 21 CFR Part 820 (Quality System Regulation)
- Reporting of Adverse Events and Recalls
- Device Labeling Provisions
 - Prohibition against misbranding, adulteration, false or misleading claims, sales of banned devices
- Maintenance of Records and Provision of reports to FDA

Class II IVDs

- Moderate risk devices, tend to be more complex
- Examples:
 - factor deficiency test
 - antimicrobial susceptibility test systems
 - thyroid stimulating hormone test system
- Premarket Notification [510(k)]
- Special Controls
- General Controls

Premarket Notification: 510(k)

- 510(k) submission required of most class II devices
- Submission has 90 day review clock
- FDA clearance based on “substantial equivalence” to legally marketed device (predicate device)
- What substantial equivalence to predicate device means:
 - Similar intended use
 - Similar performance characteristics
- What substantial equivalence does NOT mean
 - Identical technology
- Submissions may require clinical data
- Summary of FDA’s review and basis for decision is posted on the FDA website

Special Controls

- What they are:
 - Special requirements for devices when the general controls alone are insufficient
 - May include:
 - special labeling requirements
 - mandatory performance standards
 - postmarket surveillance
- Special controls are described through guidance documents which are posted on FDA's website

Class III IVDs

- Represent highest risk, most complex devices, novel intended uses

Examples:

- Hepatitis B and C, HPV tests
- Total PSA for prostate cancer screening
- Continuous Glucose Monitoring Devices
- Premarket Application [PMA]
- Submissions often include clinical data

Premarket Application (PMA)

- 180 day review clock
- Demonstration of safety and effectiveness
- Does not use predicates
- Submissions often include clinical data
- Pre-approval inspection performed
- FDA may seek may require advisory panel decision prior to approval
- Summary of Safety and Effectiveness Data (SSED) posted publicly on web

De novo

- Used for devices:
 - that do not have a legally marketed predicate
 - are not high risk
 - the risks that do exist can be mitigated through Special Controls
- Reviewed for safety and effectiveness
- Used as a mechanism for down classification of devices
 - Special controls implemented
 - Classification published
 - De novo device becomes predicate for future devices of same type with same intended use
- Has been an important tool for novel IVDs

Investigational Status Devices

- Most IVD investigations are exempt
 - If test does not introduce energy into a subject
 - If test results not returned to patient/physician
 - If no invasive measures needed to get sample or samples has been obtained from another procedure

- Investigational Device Exemption (IDE)
 - Required for non-exempt devices
 - Submission required for devices for which safety and effectiveness data is being gathered
 - 30-day review clock
 - Must be labeled for investigational use
 - Informed consent for samples
 - IRB approval of study



Premarket Review

All IVDs must establish adequate:

Analytical Validity

- How accurately does the test measure the analyte?
- How reliably?

Clinical performance

- How reliably does the test measure the clinical condition?

Labeling (21 CFR 809.10)

- Adequate instructions for use
- Intended use, directions for use, warnings, limitations, interpretation of results, performance summary

Analytical Performance

- FDA recommends use of CLSI evaluation protocols to evaluate device performance
- Assess:
 - Repeatability/Reproducibility
 - Accuracy
 - “Truth” – may be a reference method, clinical endpoint, predicate device, etc...
 - Limit of Detection/Limit of Quantitation
 - Linearity
 - Potential Interferences/ Cross-Reactivity
 - Cross-contamination / Carry-over
 - Matrix effects
 - etc...

Clinical Performance

- Clinical Validity
 - Device must have a clinical indication
 - Device should add value to clinical management
- Clinical validity claims may be based on:
 - Existing clinical data (i.e. no new clinical data needed)
 - E.g. Sodium
 - New clinical trial data
 - Review of information in the literature
 - Current clinical knowledge

Clinical Performance

- Retrospective studies OK? Yes – *IF*:
 - the study supports the intended use of the test
 - samples were collected and stored appropriately in a manner that reflects current practice
 - no sampling bias
- Literature to support device
 - All published studies should be analyzed for their applicability to the device claims

Clinical Performance

- If a new clinical study is needed. . .
 - Study should clearly define samples/populations
 - Should represent Intended Use population
 - Prospectively collected (ideal)
 - Clearly defined inclusion/ exclusion criteria
 - Sample size/trial design statistically appropriate
 - Review of new clinical studies
 - Team of experts included in review e.g. statisticians, physicians
 - Use clinical practice and society guidelines in decision-making process
 - Often include input from outside experts, advisory panels as needed



Software/Instruments

- FDA regulates all software/instrumentation used in diagnostic test systems
- Total system validation
- Database integrity
- Cyber-security
- FDA has guidance on how to validate, present data for software:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089543.htm>

Quality System Regulation (QS Reg)

- As per 21 CFR Part 820
 - Requires that manufacturers have an **appropriate** quality system and policies in place for their manufacturing operation
 - Regulation designed to be flexible for both large and small manufacturers
 - Appropriate trained personnel and facilities
 - Controlled
 - device design
 - purchasing, installation, and distribution
 - manufacture, packaging, labeling, storage, etc
 - Correction and prevention system
 - Complaint handling
 - Documentation

Medical Device Reports (MDRs)

- Reports to FDA by user facility/manufacturer when a device:
 - Caused or contributed, or may have caused or may have contributed to a death
 - Caused or contributed, or may have caused or may have contributed to a serious injury
 - Malfunctioned or failed to meet specifications (manufacturer only)
 - Recurrence could result in death or serious injury
- Required timeframe for reporting
 - 5-30 days, depending on severity
 - Follow-ups when needed
- FDA assesses reports and decides if action is needed

Recalls

- Method of removing or correcting products that are in violation of laws
- Products present a risk of injury or gross deception or are otherwise defective
- Usually voluntary by manufacturer, but must be reported to FDA
- FDA
 - Conducts health hazard evaluation (HHE)
 - Classifies recall
 - Posts recall information on website
 - Ensures manufacturer completes recall



FDA Enforcement

- Carries out inspections of manufacturing facilities
- Acts on findings and allegations of violative activities

PreIDE Meetings

- Can be requested to discuss any future submission (not just IDEs)
- Informal review of sponsors' proposed intended use, IVD validation plans, etc.
 - Flexible process
 - Not binding on FDA or sponsor
 - Can help sponsors refine intended use, and study designs
 - Good option for new sponsors, new tests
 - Can be a single interaction or multiple cycles



FDA Outreach

- 510(k) Workshop
 - OIVD participates in this each year to foster communication between the professional, manufacturing and regulatory communities
 - Provides education on submission requirements and strategies
 - Sessions led by FDA personnel who review 510(k) submissions
- FDA participation in workshops and conferences put on by device and medical societies
- FDA is willing to hold additional education and outreach workshops as needed

Small Manufacturers Assistance

- Division of Small Manufacturers, International and Consumer Assistance (DSMICA)
 - Provide assistance and guidance on pre- and post-market issues
 - Contact information:
 - Email: dsmica@fda.hhs.gov
 - Phone: 1-800-628-2041

Information on Cleared/Approved IVDs

- OIVD Review Decision Summary
 - Standard template with review data for 510(k)s
- 510(k) database
 - <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm>
- PMA Safety and Effectiveness Summary
 - <http://www.fda.gov/cdrh/pmapage.html>
- For de novo 510(k)s, Special Controls Guidance Documents available
 - Describes 510(k) submission requirements for devices of same type with same/similar intended use
 - <http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/default.htm>



Accessing Review Decision Summaries

510(k) database:

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm>

The screenshot shows the FDA's 510(k) Premarket Notification search interface. At the top, there is a navigation bar with the FDA logo and the text "U.S. Food and Drug Administration". Below this is a search bar with an "A-Z Index" button and a "Search" input field. The main content area is titled "510(k) Premarket Notification" and includes a "CDRH SuperSearch" logo. A navigation menu lists various categories: Home, Food, Drugs, Medical Devices, Vaccines, Blood & Biologics, Animal & Veterinary, Cosmetics, Radiation-Emitting Products, and Tobacco Products. The search form itself is titled "Search 510(k) Database" and includes fields for "510K Number" (with "K" entered), "Type", "Model", "Applicant Name", "Device Name", "Panel", "Decision", "Decision Date" (with a date range selector), and "Sort by" (set to "Decision Date (descending)"). There are also checkboxes for "Cleared/Approved IVD Products", "Expedited Review", "Third Party Reviewed", and "Clinical Trials", along with a "Product Code" field. A footer note states: "For full-text search, select Go To Simple Search button".



Accessing Review Decision Summaries

New Search		Back To Search Results	
510(k) Premarket Notification Database			
Device Classification Name		Classifier, Prognostic, Recurrence Risk Assessment, Rna Gene Expression, Breast Cancer	
510(K) Number		K062694	
Device Name		MAMMAPRINT	
Applicant		AGENDIA BV Louwesweg 6 Amsterdam, NL 1066 EC	
Contact		Guido Brink	
Regulation Number		866.6040	
Classification Product Code		NYI	
Date Received		09/11/2006	
Decision Date		02/06/2007	
Decision		Cleared For Marketing Automatic Class Iii Designat (AN)	
Classification Advisory Committee		Immunology	
Review Advisory Committee		Immunology	
FOI ITEM		LETTER	
FDA Review Type		Decision Summary	
Reviewed By Third		Cleared For Marketing Automatic Class III Designation	



Review Decision Summaries

Decision Summary contains the information used to support clearance:

**510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY**

A. 510(k) Number:

k062694

B. Purpose for Submission:

New device

C. Measurand:

70 gene expression profile

D. Type of Test:

Expression microarray

Test service performed in a single laboratory in Agendia's Amsterdam facility.

E. Applicant:

Agendia BV

F. Proprietary and Established Names:

MammaPrint®

G. Regulatory Information:

1. Regulation section:

21 CFR 866.6040 Gene expression profiling test system for breast cancer prognosis

2. Classification:



Accessing Summary of Safety and Effectiveness

PMA Database:

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm>

PMA - Premarket Approval



[510\(k\)](#) | [Registration & Listing](#) | [Adverse Events](#) | [Recalls](#) | [PMA](#) | [Classification](#) | [Standards](#)
[CFR Title 21](#) | [Radiation-Emitting Products](#) | [X-Ray Assembler](#) | [Medsun Reports](#) | [CLIA](#)

Search PMA - Premarket Approval [Help](#) | [Download Files](#) | [More about PMA](#)

Applicant Name	<input type="text"/>	Docket Number	<input type="text"/>
Trade Name	<input type="text"/>	Expedited Review	<input type="button" value="v"/>
Decision Date	<input type="text"/> to <input type="text"/>	Product Code	<input type="text"/>
Notice Date	<input type="text"/> to <input type="text"/>	PMA Number	<input type="text" value="P"/>
Advisory Committee	<input type="button" value="v"/>	Cleared/Approved IVD Products	<input type="checkbox"/>
Supplement Type	<input type="button" value="v"/>		
Sort by	<input type="button" value="v"/> Decision Date (Descending)		

For full-text search, select [Go to Simple Search](#) button



Accessing Summary of Safety and Effectiveness

[New Search](#) [Back to Search Results](#)

Note: this medical device has supplements. The device description may have changed. Be sure to look at the supplements to get an up-to-date view of this device.

Trade Name	CONTINUOUS GLUCOSE MONITORING SYSTEM
Classification Name	Sensor, Glucose, Invasive
Generic Name	Continuous Subcutaneous Glucose Monitoring Sytem
Applicant	MEDTRONIC MINIMED
PMA Number	P980022
Date Received	12/15/1997
Decision Date	06/15/1999
Product Code	MDS [Registered Establishments With MDS]
Docket Number	99M-2169
Notice Date	07/14/1999
Advisory Committee	Clinical Chemistry
Expedited Review Granted?	Yes
Information About:	Labeling, Approval Order, Summary Of Safety And Effectiveness

Approval Order Statement
The device is intended to continuously record interstitial glucose levels in persons with diabetes mellitus. This information is intended to supplement, not replace blood glucose information obtained using standard home glucose monitoring devices. The information collected by the device may be downloaded and displayed on a computer



Summary of Safety and Effectiveness

- General information
- Indications for Use
- Device Description
- Contraindications, Warnings, and Precautions
- Alternative Practices and Procedures
- Marketing History
- Potential Adverse Effects of the Device on Health
- Summary of Preclinical Studies
- Summary of Clinical Studies
- Conclusions Drawn from the Studies
- Panel Recommendations
- CDRH Decision
- Approval Specifications

Resources: Guidance Documents

- Provides the agency's current thinking on a topic
- Initially issued in draft form, allow for public comment
- Examples of guidance documents:
 - In Vitro Diagnostic Device (IVD) Studies – Frequently Asked Questions
 - Statistical Guidance on Reporting Results from Studies Evaluating Diagnostic Tests
 - Guidance for the Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable



On-Line Resources: OIVD Webpage

- Access information relevant to IVDs
 - Regulations
 - Guidances
 - CLIA categorizations
 - Standards
 - Lab and user information

<http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/default.htm>

On-Line Resources: CDRH Device Advice

- Website with information on medical devices
 - Guidance
 - Regulations
 - Databases
- Good place to look for explanations of how to make submissions, pre- and post-market requirements
- <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/default.htm>



Thank you!